

New Medications in Glaucoma

What might be coming to a pharmacy near you?

BY GARY D. NOVACK, PhD

In late October 2007, the FDA approved Combigan (brimonidine tartrate, 0.2% timolol maleate, 0.5% ophthalmic solution; Allergan, Inc., Irvine, CA). The most recently approved new chemical entities (the pharmaceutical industry's term for new molecules) in the US for the treatment of elevated IOP, however, are Lumigan (bimatoprost ophthalmic solution; Allergan, Inc.) and Travatan (travoprost ophthalmic solution; Alcon Laboratories, Inc., Fort Worth, TX) in March 2001. This article discusses various products in research and development for the treatment of glaucoma and ocular hypertension.

METHODS

I defined a new medication as one that was not yet available in all major countries. For sources, I used published articles, meeting abstracts, press releases, companies' Web sites, and a clinical trial registry (<http://www.clinicaltrials.gov>). I also contacted senior management from worldwide ophthalmic pharmaceutical firms for information that was not confidential.

Readers should be aware that molecular names and numbers change during development, and thus it is possible that the same product may be presented under different names. Also, although companies may make public their initial efforts on a compound, they may not always publicize their decision to pause or stop work in this area. It therefore is not possible to be completely comprehensive in this list.

The information in this report is current as of October 2007. I categorize the treatments by their chemical class and discuss neuroprotection.

PROSTAGLANDIN ANALOGS

Four prostaglandin analogs are approved in most countries: Travatan; Lumigan; Xalatan (latanoprost; Pfizer Inc., New York, NY); and Rescula (unoprostone; Uneo, Tokyo, Japan). Several new prostaglandin analogs are in various stages of development (Table 1).

"Fortunately for glaucoma clinicians, the pharmaceutical treatment of glaucoma is an area that is currently actively researched and funded."

Aerie Pharmaceuticals, Inc. (Bridgewater, NJ), is developing a novel prostaglandin analog, AR-102, that has 150-fold greater selectivity and 30-fold greater potency at the FP receptor than latanoprost. In preclinical studies, the drug has shown greater IOP-lowering efficacy and a longer duration of action than latanoprost and better ocular tolerability than travoprost. AR-102 is currently in early-stage clinical development.

Alcon Laboratories, Inc., is continuing to develop Travatan Z in countries accepting the USP antimicrobial effectiveness test.¹ This formulation of travoprost is preserved with Sofzia (Alcon Laboratories, Inc.), a combination of zinc, borate, propylene glycol, and sorbitol.

Ista Pharmaceuticals, Inc. (Irvine, CA), licensed a new formulation of latanoprost from Senju Pharmaceuticals Co., Ltd. (Osaka, Japan).

Pfizer Inc. and NicOx SA (Sophia Antipolis, France) have a prostaglandin F_{2α} analog with nitric oxide-donating properties, PF-03187207, in phase 2 clinical trials.

Santen, Inc. (Napa, CA), is developing tafluprost (DE-085). The drug was submitted for marketing approval in Japan in July 2006 and in Europe in April 2007.

RHO-KINASE INHIBITORS

Rho-kinase is an enzyme that phosphorylates cytoskeletal regulatory proteins and may play a role in cytoskeletal regulation. Several companies are conducting clinical or late-stage preclinical evaluations of molecules that inhibit Rho-kinase (Table 1).

TABLE 1. MAJOR CLASSES OF PHARMACEUTICAL GLAUCOMA THERAPIES IN RESEARCH AND DEVELOPMENT

Product	Company
Prostaglandins	
AR-102	Aerie Pharmaceuticals, Inc. (Bridgewater, NJ)
Travatan Z (available in the US)	Alcon Laboratories, Inc. (Fort Worth, TX)
Latanoprost reformulation	Ista Pharmaceuticals, Inc. (Irvine, CA)
PF-03187207	Pfizer Inc./NicOx SA (New York, NY/Sophia Antipolis, France)
Tafluprost	Santen, Inc. (Napa Valley, CA)
Neuroprotection	
Memantine	Allergan, Inc. (Irvine, CA)
Growth factors	Neurotech USA, Inc. (Lincoln, RI)
SRT501	Sirtris Pharmaceuticals, Inc. (Cambridge, MA)
TGF-Beta-Shield	Resverlogix Corp. (Calgary, Alberta, Canada)
β -amyloid inhibitors	University College in London
Epigallocatechin gallate	Academic, sponsored by the Catholic University of the Sacred Heart in Rome
Rho-kinase inhibitors	
SNJ-1656	Senju Pharmaceuticals Co., Ltd. (Osaka, Japan)
K-115	Kowa Pharmaceutical Co., Ltd. (Nagoya, Japan)
DE-104	Santen, Inc./Ube (Napa, CA/Tokyo, Japan)
Unnamed	Inspire Pharmaceuticals, Inc. (Durham, NC)
Steroids	
Anecortave acetate	Alcon Laboratories, Inc.
Mifepristone	pSivida (Perth, Western Australia)
Fixed-combination products	
Xalcom	Pfizer Inc.
DuoTrav	Alcon Laboratories, Inc.
Ganfort	Allergan, Inc.
Combigan	Allergan, Inc.
Brinzolamide/Timolol	Alcon Laboratories, Inc.

Senju Pharmaceuticals Co., Ltd., is developing SNJ-1656 and reported phase 1 results.² The active molecule in SNJ-1656 is Mitsubishi Pharma Corporation's (Osaka, Japan) Y39983. Novartis International AG (Basel, Switzerland) has a global development agreement with Senju Pharmaceuticals Co., Ltd., on this product.

Kowa Pharmaceutical Co. Ltd. (Nagoya, Japan) reported on the ocular hypotensive activity of topical K-115 in an animal model. The molecule is in phase 1 clinical trials.³

Santen, Inc., and Ube Industries (Tokyo, Japan) are jointly developing DE-104 as an ophthalmic solution.

Inspire Pharmaceuticals, Inc. (Durham, NC), has an active, ongoing Rho-kinase program, and the company is planning to begin clinical trials of a compound in 2008.

STEROIDS

Investigators are testing two different approaches to the treatment of glaucoma with molecules that have a steroid's structure (Table 1).

Alcon Laboratories, Inc., developed anecortave acetate, an angiostatic cortisene without typical corticosteroid effects,⁴ for posterior juxtasclear injection in the treatment of choroidal neovascularization due to age-related macular degeneration.⁵ The drug (Retaane) is approved in Australia for this indication. The company is also investigating the drug's potential use as an ocular hypotensive agent by sub-Tenon's injection. Anecortave acetate was more effective than its vehicle for 3 months after a single injection.⁶

pSivida (Perth, Western Australia) is conducting phase 2

TABLE 2. PHARMACEUTICAL GLAUCOMA THERAPIES IN RESEARCH AND DEVELOPMENT: OTHER AGENTS IN CLINICAL DEVELOPMENT

Company	Compound	Status
Acadia Pharmaceuticals Inc. (San Diego, CA)	Selective muscarinic compound	Phase 1
Alcon Laboratories, Inc. (Fort Worth, TX)	AL-37807 (undisclosed structure or mechanism)	Phase 2
Biovitrum AB (Stockholm, Sweden)	BVT.28949 (5-HT _{2A} receptor antagonist)	Phase 2a
Danube Pharmaceuticals, Inc. (New York, NY)	DNB-001 "a novel oral therapy with a dual mechanism of action"	Phase 2
Merck & Co, Inc. (Whitehouse Station, NJ)	C-3859 (undisclosed structure or mechanism)	Phase 1
Santen, Inc. (Napa, CA)	Olmesartan (DE-092; angiotensin II antagonist)	Phase 2
Santen, Inc.	Lomerizine (DE-090; calcium channel blocker to improve blood flow, in-licensed from Nippon Organon KK [Osaka, Japan]).	Phase 2

development of mifepristone (RU-486, a corticosteroid receptor antagonist) as an eye-drop treatment for corticosteroid-associated elevated IOP.

OTHER AGENTS

A host of other agents in clinical or preclinical development (Tables 2 and 3) cover a wide range of mechanisms, from muscarinic agonism (eg, pilocarpine) to the alteration of the trabecular meshwork. In addition, there are two studies not under corporate sponsorship.

Researchers at the Grewal Eye Institute in Chandigarh, India, are studying bevacizumab (Avastin; Genentech, Inc., South San Francisco, CA) by subconjunctival injection for the prevention of bleb failure after glaucoma filtration surgery. In addition, investigators at the Federal University of São Paulo in Brazil are studying the use of triamcinolone acetonide (Kenalog; Bristol-Myers Squibb Company, New York, NY) in glaucoma filtering surgery.

FIXED-COMBINATION PRODUCTS

A critical advantage of fixed-combination products is that they present a simpler regimen for the patient than two separate bottles. Recent electronic monitoring data have shown that more complex dosing regimens result in poorer adherence to prescribed therapy, although drugs dosed q.d. in a complex dosing regimen were found to have good adherence.⁷ There are substantial regulatory hurdles for the approval of combination products (eg, 21 CFR 300.50 in the US and CPMP/EWP/240/95 in the European Union).

Three prostaglandin combinations are approved in some major markets, although not in the US, where they have "approvable" status⁸:

- latanoprost and timolol (Xalcom, Xalacom; Pfizer Inc.);
- travoprost and timolol (DuoTrav; Alcon Laboratories, Inc.); and

- bimatoprost and timolol (Ganfort; Allergan, Inc., Irvine, CA).

As noted earlier, Combigan is approved in the US as well as in most of the rest of the world. Alcon Laboratories, Inc., is developing a combination of brinzolamide and timolol.

NEUROPROTECTION

Regulatory agencies in the major developed nations approve therapeutic pharmacological agents to treat glaucoma based upon their effects on lowering IOP. This policy is based upon the premise that lowering elevated IOP is a surrogate for attenuating glaucomatous visual field progression. The relationship between IOP and perimetric progression has been demonstrated by many major studies.⁹⁻¹⁴ Several firms are evaluating molecules for their ability to reduce progression independent of their ocular hypotensive effect (Table 1).

Allergan, Inc., conducted two studies assessing the effect of oral memantine in addition to ocular hypotensive medications to slow glaucomatous visual field loss. According to a published statement from the company, "The functional measure chosen as the primary endpoint did not show a benefit of memantine in preserving visual function. In a number of analyses using the secondary functional measure, memantine demonstrated a statistically significant benefit of the high dose compared to placebo." Additional analysis was ongoing as of January 2008.

Neurotech USA, Inc. (Lincoln, RI), has a core technological platform called Encapsulated Cell Technology. This intravitreal implant allows for the long-term, sustained delivery of therapeutic growth factors to the posterior pole. The firm plans to evaluate this technology for glaucoma in the future.

SRT501 (resveratrol, Sirtris Pharmaceuticals, Inc.; Cambridge, MA) was reported effective in a murine model of optic neuritis.¹⁵

Resverlogix Corp. (Calgary, Alberta, Canada) is evaluat-

TABLE 3. PHARMACEUTICAL GLAUCOMA THERAPIES IN RESEARCH AND DEVELOPMENT: OTHER AGENTS IN PRECLINICAL DEVELOPMENT (OR UNKNOWN STAGE)

Company	Compound	Status
Alacritty Biosciences (Laguna Hills, CA)	ALTY-0601 is a small synthetic peptide molecule, which competitively binds the cell receptor for fibronectin. The proposed mechanism is binding to fibronectin in the trabecular meshwork to increase outflow.	An investigational new drug application is planned in the first part of 2008.
Allergan, Inc. (Irvine, CA)	Sphingosine-1-phosphate agonists	Patent application(s) filed
Inspire Pharmaceuticals, Inc. (Durham, NC)	INS115644, a compound that actively disrupts the actocytoskeleton of the trabecular meshwork (in-licensed from the Wisconsin Alumni Research Foundation) ¹⁶	N/A
Ista Pharmaceuticals, Inc. (Irvine, CA)	Iganidipine (calcium channel blocker, from Senju Pharmaceuticals Co, Ltd. [Osaka, Japan])	N/A
Merck & Co, Inc. (Whitehouse Station, NJ)	Calcium-activated K ⁺ (maxi-K) channel blockers	N/A
NicOx (Sophia Antipolis, France)	Nitro-oxo-analogs of apraclonidine/brimonidine	Patent application(s) filed
Novagali Pharma SA (Evry, France)	Nova21027 (next-generation, preservative-free glaucoma treatment)	N/A
Novartis International AG (Basel, Switzerland)	KRG-3332 (highly selective α_{1A} receptor antagonist from Kissei Pharmaceutical Co, Ltd, Nagano Prefecture, Japan)	N/A
Othera Pharmaceuticals Inc. (Exton, PA)	OT-730 (a small molecule, oculoselective β -adrenoceptor antagonist)	N/A
Pfizer Inc. (New York, NY)	Collaborative agreement with pSivida (Perth, Western Australia) on controlled drug delivery technologies, including Medidur	N/A
QLT Inc. (Vancouver, British Columbia, Canada)	Drug delivery system using a punctal plug for drug delivery from ForSight Laboratories (Menlo Park, CA)	N/A
NOTE. The status of development is presented, if known. N/A, not applicable.		

ing TGF-Beta Shield in preclinical models.

Morrison et al found a role for β -amyloid in neuronal apoptosis in a rat model of glaucoma,¹⁷ and Guo et al were able to attenuate retinal ganglion cell loss by inhibiting different components of the formation and aggregation pathway of β -amyloid.¹⁸

Epigallocatechin gallate, a flavinoid, given orally, is being evaluated for its effects on the function of retinal ganglion cells in work sponsored by the Catholic University of the Sacred Heart in Rome.

Although there are many mechanisms under investigation for neuroprotection in glaucoma and despite positive animal data, unfortunately, there are no approved products at this time. Neurologists saw failures in three recent

trials of potential neuroprotective agents. A mixed-lineage kinase inhibitor, CEP-1347, failed to delay disability in early Parkinson's disease.¹⁹ Transdermal selegiline failed to slow HIV-associated cognitive impairment.²⁰ Lastly, chronic oral minocycline was actually worse than placebo in a trial involving patients with amyotrophic lateral sclerosis.²¹

CONCLUSION

The development of new pharmaceutical products is a long-term, highly expensive, extremely risky endeavor. Fortunately for glaucoma clinicians, the pharmaceutical treatment of glaucoma is an area that is currently actively researched and funded. Investigators are studying

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numerous new chemical entities, fixed combinations, and novel drug delivery products, many of which—one hopes—will become approved products available for widespread use. □

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Gary D. Novack, PhD, is President of PharmaLogic Development, Inc., in San Rafael, California. He consults with numerous pharmaceutical firms, including some of those mentioned in this article and owns stock in Inspire Pharmaceuticals, Inc. Dr. Novack may be reached at (415) 472-2181; gary_novack@pharmalogic.com.



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